UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/691,157 | 10/22/2003 | Istvan Boldogh | 265.00440101 | 6536 |

26813 7590 03/02/2006

MUETING, RAASCH & GEBHARDT, P.A.
P.O. BOX 581415
MINNEAPOLIS, MN 55458

| EXAMINER | |
|---|---|
| KAM, CHIH MIN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1656 | |

DATE MAILED: 03/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/691,157 | BOLDOGH ET AL. | |
| | Examiner | Art Unit | |
| | Chih-Min Kam | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-7 are pending.

Applicants' amendment filed August 29, 2005 is acknowledged. Applicants' response has been fully considered. Claims 1, 6 and 7 have been amended, and claims 8-9 have been cancelled. Therefore, claims 1-7 are examined.

### ***Withdrawn Informalities***

2. The previous objection to the specification regarding web address is withdrawn in view of applicants' amendment to the specification in the amendment filed August 29, 2005.

### ***Withdrawn Claim Objections***

3. The previous objection to claims 6-7 regarding the recitation of non-elected sequences in the claims, is withdrawn in view of applicants' amendment to the claim in the amendment filed August 29, 2005.

### ***Withdrawn Claim Rejections - 35 USC § 112***

4. The previous rejection of claims 1-7, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 8-11 in the amendment filed August 29, 2005.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating an intracellular signaling

molecule in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide of colostrinin with a defined sequence (i.e., SEQ ID NOs:1-8), or a combination thereof, wherein the modulator reduces 4HNE-protein adduct formation, inhibits 4HNE-mediated glutathione depletion, inhibits 4HNE-mediated activation of p53 protein, or inhibits 4HNE-induced activation of c-Jun N-terminal kinases; or a method of down regulating the 4HNE mediated oxidative damage associated with lipid peroxidation in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide of colostrinin with a defined sequence (i.e., SEQ ID NOs:1-8), or a combination thereof, does not reasonably provide enablement for a method of modulating an intracellular signaling molecule in a cell, or a method of down regulating the HNE mediated oxidative damage associated with lipid peroxidation in a cell, the method comprising contacting the cell with a modulator, wherein the modulator is an active analog of a constituent peptide of colostrinin, and wherein the active analog comprises a peptide having an amino acid sequence with at least 15 percent proline and having at least 70 percent sequence identity (or sequence similarity) to a constituent peptide of colostrinin of SEQ ID NO:1-8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-5 and 7 encompass a method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated oxidative damage associated with lipid peroxidation in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof. The specification, however, only discloses cursory conclusions (page 2-4), which state that the

present invention provides a method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated lipid peroxidation in a cell, comprising contacting the cell with colostrinin, a constituent peptide, an active analog or combinations thereof, where the active analog is an active analog of a constitute peptide of colostrinin selected from the group of SEQ ID NO:1-34, and the active analog comprises a peptide having an amino acid sequence with at least about 15% proline and having at least 70 % structural similarity to one or more constituent peptides of colostrinin. There are no indicia that the present application enables the full scope in view of the use of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof in the claimed method as discussed in the stated rejection. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the active analogs of the constituent peptides of colostrinin of SEQ ID NO:1-8 that comprises a peptide having an amino acid sequence with at least about 15% proline and having at least 70 % structural similarity to SEQ ID NO:1-8, which are not adequately described or demonstrated in the specification.

(2). The presence of absence of working examples:

The specification has shown colostrinin reduces 4HNE-protein adduct formation in PC 12 cells (Example 1); colostrinin affects the oxidative metabolism and protects the oxidative stress induced by 4HNE in PC 12 cells (Example 2); Effects of colostrinin on 4HNE-induced loss of intracellur GSH levels (Example 3); 4HNE-induced activation of JNK is suppressed by colostrinin (Example 4); and colostrinin inhibits 4HNE-induced activation of p53 (Example 5). However, there are no working examples identifying the active analogs that are functional in the claimed methods.

(3). The state of the prior art and relative skill of those in the art:

The related art indicates colostrinin and its fragment are useful for treating disorders of central nervous system, neurological disorders and neurodegenerative disorders and a composition comprising colostrinin or its constituent peptide is prepared (page 1, lines 29-page 2, line 5 of the instant application; WO 98/14473), and considerable evidence has indicated increased oxidative stress may play a role in the pathogenesis of neuron degeneration and death in the neurodegenerative disorders (Markesbery, Free Radical Biology & medicine 23, 134-147 (1997)). However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identification of active analogs of the constituent peptides of colostrinin in the claimed method to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated oxidative damage associated with lipid peroxidation in a cell, the method comprising contacting the cell with a modulator selected from the group of

colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof. However, the specification has not provided sufficient teaching on identification of the active analogs, and their effects in 4HNE-mediated biological processes. Active analogs of constituent peptides of colostrinin are broadly defined as comprising a peptide having an amino acid sequence with at least about 15% proline and having at least 70 % structural similarity to the constituent peptides in the specification (page 12, lines 9-14), which would encompass numerous peptide sequences. Since the specification does not identify any active analog for the constituent peptide of SEQ ID NO:1-8, it is unpredictable regarding the amino acid sequences of these analogs.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of modulating an intracellular signaling molecule or down regulating 4HNE-mediated oxidative damage associated with lipid peroxidation in a cell, the method comprising contacting the cell with a modulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof. While the specification shows colostrinin reduces 4HNE-protein adduct formation in PC 12 cells (Example 1); colostrinin affects the oxidative metabolism and protects the oxidative stress induced by 4HNE in PC 12 cells (Example 2); Effects of colostrinin on 4HNE-induced loss of intracellur GSH levels (Example 3); 4HNE-induced activation of JNK is suppressed by colostrinin (Example 4); and colostrinin inhibits 4HNE-induced activation of p53 (Example 5), the specification does not identify any active analog of the constituent peptide of colostrinin. Furthermore, there are no examples demonstrating the effects of various active analogs of

constituent peptides in the claimed method. Since the specification does not provide sufficient teachings on the identities of various active analogs and the effects of various active analogs in the claimed methods, it is necessary to carry out undue experimentation to identify the active analogs of the constituent peptides and to assess their effects in modulating 4HNE-mediated process in cells.

(6). Nature of the Invention

The scope of the claims includes many structural variants for active analogs of the constituent peptides of colostrinin, but the specification does not provide sufficient teachings on the identities and effects of these analogs in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods associated with the variants, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out undue experimentation to identify the active analogs of the constituent peptides of colostrinin in the claimed methods.

*Response to Arguments*

Applicants indicate claims 1-5 and 7 have been amended to recite the constituent peptides of colostrinin consisting of SEQ ID NO: 1-8 and the active analogs of a constituent peptide of colostrinin have "an amino acid sequence with at least about 1 5 percent proline and having at least about 70 percent structural similarity to a constituent peptide of colostrinin of SEQ ID NO: 1-8. The specification have provided the amino acid sequences of the constituent peptides of colostrinin (SEQ ID NOs: 1-8; page 10, lines 5-10), as well as guidance for active analogs of

constituent peptides of colostrinin having an amino acid sequences with at least about 15 percent praline (see page 12, lines 9-14), and having at least about 70 percent structural similarity to one of constituent peptides SEQ ID NOs: 1-8 (see page 12, lines 29-33). Thus, it is routine for one of skill in the art to make and use the claimed constituent colostrinin peptides and active analogs thereof base on the teachings of the specification. Claim 7 has been amended to recite a "method of down regulating the 4-HNE-mediated oxidative damage associated with lipid peroxidation in a cell." As explained in the specification, 4HNE is a 3'-unsaturated aldehyde generated endogenously during lipid peroxidation in a cell (page 23, lines 8-9), and Example 2, (see page 18, line 30 to page 19, line 8; page 20, line 30 to page 21, line 17; page 23, lines 6-11) demonstrating the protective effects of colostrinin, constituent peptides, or an active analog thereof against the oxidative damage induced of 4HNE exposure. Thus, the specification provides adequate instruction to allow one of skill in the relevant art to practice the claimed method of down regulating the 4HNE-mediated oxidative damage associated with lipid peroxidation in a cell (pages 6-8 of the response).

Applicants response has been considered. Regarding using the constituent peptides of SEQ ID NO:1-8 in the claimed method, and the method of down regulating the 4-HNE-mediated oxidative damage associated with lipid peroxidation in a cell using colostrinin, or a constituent peptide of SEQ ID NOs:1-8, the argument is persuasive, thus the rejection is withdrawn. However, regarding the active analogs of the constituent peptides of SEQ ID NO:1-8 used in the claimed method, the argument is not found persuasive because the active analogs, which have been broadly defined in the specification and encompass numerous peptide sequences, are not identified, and their effects in the claims are not demonstrated, thus, it is required undue

experimentation to identify the active analogs of the constituent peptides of SEQ ID NO:1-8 and to assess their effects in the claimed method. Therefore, the full scope of the claim is not enabled.

6. Claims 1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1-5 and 7 are directed to a method of modulating an intracellular signaling molecule in a cell, or a method of down regulating the 4HNE mediated oxidative damage associated with lipid peroxidation in a cell, the method comprising contacting the cell with an effective amount of colostrinin, a constituent peptide of colostrinin, an active analog of a constituent peptide of colostrinin, and combinations thereof, wherein the constituent peptide of colostrinin is selected from the group consisting of SEQ ID NO:1-8, and wherein the active analog of a constituent peptide of colostrinin comprises a peptide having an amino acid sequence with at least 15 percent proline and having at least 70 percent sequence identity (or sequence similarity) to a constituent peptide of colostrinin of SEQ ID NO:1-7 or 8. While the specification discloses SEQ ID NO:4 has amino acid sequence LFFFLPVVNVLP and SEQ ID NO:8 has amino acid sequence LKPFPKLKVEVFPFP (page 10, lines 7-9; sequence listing), the specification does not indicate LFFFLPVGVLP is SEQ ID NO:4 and LKPFPCKVEVFPFP is SEQ ID NO:8 as recited in the claims (see claim 1, lines 14 and 21; claim 7, lines 12 and 14). The lack of description of SEQ ID NO:4 having the sequence of LFFFLPVGVLP and SEQ ID NO:8 having the sequence of LKPFPCKVEVFPFP, applicants have failed to sufficiently

describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

***Claim Objection***

7. Claim 6 is objected to because the claim is dependent from a rejected claim.

***Conclusion***

8. Claims 1-5 and 7 are rejected; and claim 6 is objected to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
February 27, 2006